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# Conceptual disorganization and redistribution of resting state cortical hubs in drug-naive first episode psychosis: A 7T functional magnetic resonance imaging study

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Graduate Program in Neuroscience  
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## Abstract

Network level dysconnectivity has been studied in positive and negative symptoms of schizophrenia. Conceptual disorganization (CD) is a symptom which predicts impaired real-world functioning. Systematic reviews have reported aberrant connectivity in formal thought disorder, a construct related to CD. However, no studies have investigated whole-brain functional correlates of CD in psychosis. We sought to investigate brain regions explaining the severity of CD in patients with first-episode psychosis (FEPs) compared with healthy controls (HCs). We computed whole-brain binarized degree centrality maps of 31 FEPs, 25 HCs and characterized the patterns of network connectivity in the two groups. In FEPs, we related these findings to the severity of CD. We also studied the effect of positive and negative symptoms on altered network connectivity. Compared to HCs, the FEPs showed reduced hubness of a cluster located in the right superior temporal gyrus (rSTG). In patients exhibiting high CD, increased hubness of a medial superior parietal (mSPL) cluster was observed, compared to patients exhibiting low CD. These two regions were strongly correlated with CD scores but not with other symptom scores. Our observations are congruent with previous findings of reduced but not increased hubness. We observed increased hubness of mSPL suggesting that a cortical reorganization occurs in brain networks to provide alternate routes for information transfer. These findings provide insight into the underlying neural processes mediating the presentation of symptoms in untreated FEP. A longitudinal tracking of the symptom course will be useful to assess the mechanisms underlying these compensatory changes.

Keywords: conceptual disorganization, first-episode psychosis, resting-state fMRI, graph theory, cortical reorganization

## Dedication

I dedicate this thesis to my parents who have been my pillars of strength in this journey and for their unwavering love. I also dedicate this thesis to my mentor, Dr. Naren Rao, as this journey would not have been possible without his encouragement and faith in my abilities.

*“Our deepest fear is not that we are inadequate. Our deepest fear is that we are powerful beyond measure.”*

*-Marianne Williamson*

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## Table of Contents

Abstract .....	i
Table of Contents .....	v
List of Tables .....	viii
List of Figures .....	ix
List of Appendices .....	x
Chapter 1: <i>Introduction</i> .....	1
1.1 General overview .....	1
1.2 The clinical construct of psychosis – a historical overview .....	1
1.3 Definition of psychosis .....	2
1.4 Symptoms of psychosis.....	3
1.5 Persistence of the symptoms of psychosis .....	4
1.6 Conceptual disorganization in acute psychosis.....	5
1.7 Neural correlates of conceptual disorganization - a review of the neuroimaging literature .....	5
1.8 Current limitations in existing literature .....	8
1.9 Use of functional Magnetic Resonance Imaging (fMRI) as a tool to study psychosis .....	9
1.10 Description of the imaging technique(s) used in this study .....	10
1.10.1 Imaging sequences: rs-fMRI and structural MRI .....	11
1.11 Graph theoretical measures and the theory of ‘dysconnection’ in psychosis	12
1.11.1 The ‘dysconnection’ hypothesis .....	12
1.11.2 Description of graph theoretical measures used in this study.....	13
1.11.3 The methodological approach used in this study to detect altered functional connectivity with respect to conceptual disorganization ...	14
1.12 Influence of assessment procedure used to measure disorganization .....	15

1.13 Aims and Hypotheses .....	15
1.14 References .....	16
Chapter 2: <i>Manuscript</i> .....	26
2 Title: Conceptual disorganization and redistribution of resting state cortical hubs in untreated first episode psychosis: A 7T study .....	26
2.1 Authors.....	26
2.2 Author affiliations.....	26
2.3 Abstract.....	26
2.4 Keywords .....	27
2.5 Introduction.....	28
2.6 Materials and Methods.....	30
2.6.1 Participants.....	30
2.6.2 Clinical and cognitive assessments.....	31
2.6.3 MRI acquisition .....	35
2.6.4 Data preprocessing.....	35
2.6.5 Computing degree centrality maps .....	37
2.7 Statistical analysis.....	39
2.8 Results.....	40
2.8.1 Demographic and clinical characteristics .....	40
2.8.2 Effect of psychosis on bDC .....	40
2.8.3 Functional connectivity of STG/insula cluster with the rest of the brain .....	41
2.8.4 Effect of conceptual disorganization on bDC.....	43
2.8.5 Specificity of findings to disorganization.....	46
2.8.6 Discussion.....	46
2.9 References.....	49

2.10 Supplementary information .....	56
2.10.1 References:.....	62
2.11 Funding.....	63
2.12 Conflict of interest.....	63
2.13 Acknowledgements .....	63
Chapter 3: <i>General discussion</i> .....	64
3 Conclusions .....	64
3.1 References:.....	68

## List of Tables

Table 1 Demographic and clinical characteristic of the sample included for analysis in the study.....	33
Table 2 Demographic and clinical characteristics of the sample excluded from analysis in the study.....	35
Table 3 Brain regions showing reduced hubness in the FEP (n = 38) group compared to HCs (n = 31). .....	41
Table 4 Functional connectivity of the STG/insula cluster to other brain areas for subjects in the FEP group (n = 38). The colour bar indicates T-values.....	42
Table 5 Brain regions showing reduced hubness in the High P2 group (n = 12) compared to the Low P2 group (n = 26).....	44
Table 6 Functional connectivity of the medial superior parietal lobule cluster to other brain areas in the FEP group (n = 38). .....	45
Table 7 Brain regions showing wDC alterations in the FEP group (n = 38) compared to the HC group (n = 31).....	56
Table 8 Correlation between the eigenvariates of STG/Insula and mSPL clusters in the FEP group .....	59

## List of Figures

Figure 1 Steps of preprocessing performed in this study, including slice timing correction, realignment, coregistration to structural image, segmentation into GM, WM and CSF tissue classes, nuisance covariates regression, filtering, removing linear trends from data (detrending), computing DC maps in the ‘native’ space, normalization to MNI template using DARTEL information, smoothing.....	38
Figure 2 (a) Brain regions showing reduced hubness in the FEP (n = 38) group compared to HCs (n = 31) (yellow), (b) Functional connectivity of the STG/insula cluster to other brain areas for subjects in the FEP group (n = 38). The colour bars indicate T-values....	43
Figure 3 (a) Brain regions showing reduced hubness in the High P2 group (n = 12) compared to the Low P2 group (n = 26). (b) Functional connectivity of the medial superior parietal lobule cluster to other brain areas in the FEP group (n = 38). The colour bars indicate T-values. ....	45
Figure 4 Meta-analytic results (obtained from the Neurosynth database) of functional connectivity associations between the STG/Insula cluster and the rest of the brain. ....	57
Figure 5 Functional connectivity associations between the STG/Insula cluster and the rest of the brain. ....	57
Figure 6 Meta-analytic results (obtained from the Neurosynth database) of functional connectivity associations between the medial superior parietal cluster and the rest of the brain. ....	58
Figure 7 Functional connectivity associations between the medial superior parietal cluster and the rest of the brain.....	58
Figure 8 Relationship between eigenvariate of the medial superior parietal cluster and conceptual disorganization scores.....	60
Figure 9 Relationship between eigenvariate of the medial superior parietal cluster and conceptual disorganization scores.....	61

## List of Appendices

Appendix 1 Results from a two-sample t-test (FEPs vs. HC) of weighted degree centrality (wDC) maps .....	56
Appendix 2 Neurosynth meta-analyses .....	56
Appendix 3 Correlation between eigenvariate of STG/Insula and mSPL .....	58
Appendix 4 Scatterplots between the P2 scores and eigenvariate of the STG/Insula and mSPL clusters .....	59

# 1 Chapter 1: *Introduction*

## 1.1 General overview

Psychosis is a commonly occurring feature of many psychiatric, neurodevelopmental, neurological and medical conditions which is associated with a disruption of the normal functioning capabilities of the affected individuals. Observations such as reduced social or occupational participation (Arciniegas, 2015) and core clinical symptoms such as delusions, hallucinations without insight and disorder of thought processes (DSM-5; Gaebel and Zielasek, 2015) help conceptualize psychosis as a clinical feature.

## 1.2 The clinical construct of psychosis – a historical overview

The clinical construct of psychosis was first described in 1845 by an Austrian doctor, Ernst von Feuchtersleben, as a disease of the mind or ‘Geisteskrankheiten’ (Beer, 1995, 1996). The organic nature of psychosis was proposed by Flemming in his textbook ‘The Pathology and Treatment of the Psychoses’ which suggested that psychosis occurred as the result of an underlying disorder of the nervous system (neurosis) (Beer, 1996). In his characterization of the cerebral associations of consciousness, Wernicke hypothesized the splitting (‘sejunktion’) of different psychological processes (Wernicke, 1899; Beer, 1996) as the ‘psychoses’ of perception of one’s body (somatopsychoses), personality (autopsychoses) and the outside world (allopsychoses) (Beer, 1996). Around the same time, Wernicke’s conceptualization of mental illnesses (as having anatomical and physiological underpinnings) was replaced by Kraepelin’s theory of the dichotomous nature (Gaebel and Zielasek, 2015) of ‘dementia praecox’ and ‘manic-depressive insanity’ in psychosis (Leonhard, 1985). All of these theories suggested that psychosis was an organic illness. Fuerstner (1881) suggested the functional nature of psychosis, to separate it from ‘organic psychoses’ (Beer, 1995, 1996). However, until the 1920’s, there was no clear distinction between the functional and organic subtypes of psychosis. In 1924, Bumke defined organic psychosis to affect the brain tissue and functional psychosis to affect the mind (Beer, 1996). Later, Jaspers distinguished organic psychoses from functional psychoses by referring to the latter as schizophrenia, manic-depression, and epilepsy (Jaspers, 1963).

### 1.3 Definition of psychosis

Both the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA, 2013) and the International Classification of Diseases, Tenth Revision (ICD-10) (WHO, 1993) define psychosis as a loss of the sense of reality, characterized by delusions, hallucinations without insight, and disruptions in the form of thought processes. These three features have been implicated to be the ‘core’ features of psychosis (Arciniegas, 2015; Gaebel and Zielasek, 2015). Psychosis has been implicated to be a fundamental feature of schizophrenia spectrum disorders, mood and substance use disorders, as well as some neurological conditions (Arciniegas, 2015). An impaired sense of reality is of central importance among the symptoms which characterize psychosis.

Hallucinations are perceptions or experiences (e.g. hearing voices) which occur without the presence of any stimulus from the external environment. Often the individual is unable to identify the hallucinatory features of that episode. Hallucinations are mostly auditory in nature (Stephane et al., 2001; Verdoux and van Os, 2002), with some reports of visual, tactile and olfactory hallucinations (Bracha et al., 1989) as well.

Delusions are false beliefs (e.g. notions that other people are plotting against oneself) which provide evidence of distorted reality and indicate an abnormality in the content of thoughts (Andreasen et al., 1995). The person experiencing the delusions is unable to change these beliefs despite being aware of the presence of logic which contradicts these beliefs (Arciniegas, 2015).

‘Formal thought disorders (FTD)’ or disruptions in the form of thought processes commonly occur in psychosis. These disorders are generally related to observations such as taking a lot of time before speaking (retardation), not getting to the point when discussing something (tangentiality) or the tendency to offer bizarre explanations for things or events (illogicality) (WHO, 2018), to name a few. In the diagnosis of a psychotic disorder, FTD assumes greater importance over hallucinations and delusions when a psychotic episode is accompanied by disorganized behaviour, catatonia (motor and

behavioural abnormalities) and/or negative symptoms –according to the guidelines put forward in the DSM-5 (APA, 2013; Arciniegas, 2015).

## 1.4 Symptoms of psychosis

Chronic or established psychosis (e.g. schizophrenia) is a complex mental condition, which can be diagnosed at least 6 months after the first presentation of a psychotic episode (DSM-5; Thyer, 2015). A heterogenous symptom structure including positive, negative, and disorganization symptoms (Bilder et al., 1985; Kulhara et al., 1986; Liddle, 1987; Andreasen et al., 1995) characterizes the symptoms of chronic or established psychosis (schizophrenia).

*Positive symptoms* of psychosis are defined as extreme representations of psychotic features which are associated with a magnification (Andreasen et al., 1995) of normal functions (Andreasen, 1990) such as hearing or thinking. These symptoms are characterized by a distorted perception of reality and manifest as hallucinations, delusions or false beliefs, thought disorders, and motor impairments (Andreasen et al., 1995).

*Negative symptoms* are characterized by disruptions or alterations to normal emotions and behaviours which tend to have a basic underlying persistence (Andreasen et al., 1995). These symptoms include reduced spontaneity and fluency of speech or 'alogia', reduced expression of emotions through facial expressions or voice tone commonly known as 'flattened affect' or 'affective blunting', loss of a sense of pleasure or 'anhedonia', difficulty beginning and sustaining activities or 'avolition' explained as a 'loss of will or drive', loss of the ability to focus attention on a specific activity/task in a sustained manner or 'attentional impairment' and reduced social interaction (Andreasen et al., 1995).

*Disorganization* is characterized as the impairment of the form of thought processes and bizarre actions, defined as conceptual and behavioural disorganization respectively. It has been shown to be a persistent feature in both acute and chronic stages of schizophrenia (Feigenson et al., 2014). The lack of effective treatment options results in the chronicity of the different symptom domains and relates to the unrelenting characteristics of

schizophrenia (Harrow and Marengo, 1986; Andreasen and Grove; 1986; Marengo and Harrow, 1997).

## 1.5 Persistence of the symptoms of psychosis

A large number of patients with established psychosis have been reported to experience unrelenting positive symptoms despite undergoing treatments with antipsychotics (Suzuki et al., 2011, 2012). In approximately 70% of the patients undergoing treatment with antipsychotics, a short-term reduction in the severity of positive symptoms (Haro et al., 2018) has been implied (but not observed in all patients) (Menezes et al., 2006; Novick et al., 2009; Van Os and Kapur, 2009). Relapses of psychotic episodes, rehospitalization, deficits in functioning, and a reduced 'quality of life' could result from an insufficient management of positive symptoms (Lehman and Postrado, 1995; Doering et al., 1998; Norman et al., 1999, 2001; Csernansky and Schuchart, 2002; Menezes et al., 2006; Novick et al., 2009).

Negative symptoms have been shown to be present at the time of the first psychotic episode (Bobes et al., 2010), and have been shown to persist even after treatments with antipsychotics (Erhart et al., 2006). The negative symptom subtype is a predictor of poor social and occupational functioning (Novick et al., 2009; Rabinowitz et al., 2012), even after the remission of positive symptoms (Stahl and Grady, 2004; Chue and Lalonde, 2014).

Disorganization is observed to be a persistent feature in both acute and chronic stages of established psychosis (schizophrenia) (Feigenson et al., 2014). As opposed to persistent disorganization, the pathophysiology of acute disorganization has been observed during an active psychotic episode (Breier and Berg, 1999). Acute disorganization resolves in many patients over time (Andreasen, 1979; Harrow and Marengo, 1986; Harrow, Marengo & McDonald, 1986; Harvey, Earle-Boyle & Wielgus et al., 1984), and often covaries with the severity of positive symptoms. On the other hand, the symptoms of disorganization (e.g. negative FTD) seen in chronic stages often emerge as a distinct subtype of the illness (Roche et al., 2014). The persistence of disorganization despite treatment (in longitudinal cohorts) has suggested that existing treatments are not fully effective in alleviating the

symptoms of disorganization in patients with psychosis (Harrow and Marengo, 1986; Andreasen and Grove; 1986; Marengo and Harrow, 1997).

## 1.6 Conceptual disorganization in acute psychosis

Of the three major subtypes of disorganization (conceptual disorganization (CD), poor attention, difficulties related to abstract thinking) (Rocca et al., 2018), CD has been implicated in the previous literature to be a persistent feature at all phases of the illness (Feigenson et al., 2014) and related to impairments in cognition (Bleuler, 1950; Hardy-Bayle et al., 2003) and real-world functioning (Rocca et al., 2018). CD is characterized by difficulties in the goal-directed sequencing of thoughts that manifest as circumstantial, illogical or tangential speech or weakened goal of thinking (loose associations) (Kay et al., 1987). Formal thought disorder (FTD), a construct associated with disorganization, has been shown to be the strongest predictor of impaired speech and peculiar word use (Ayer et al., 2016) in first-episode psychosis. In established psychosis (schizophrenia), FTD has also been related to impaired cognitive control (Yoon et al., 2012) and impaired functioning at different phases of the illness (Roche et al., 2015; Ortiz et al., 2017). While the construct of FTD encompasses both positive (e.g. illogical, tangential, loosened speech) as well as negative (e.g. poverty of speech, reduced content of speech) FTD, the clinical construct of CD refers only to positive aspects of FTD. Of the three major impairments (neurocognition, social cognition, formal thought disorders (FTD)) related to CD, FTD is the most extensively studied feature which is characterized by deficits in thought processes manifesting as speech disorders (eg. illogicality, retardation, tangentiality). Longitudinal studies have reported FTD to be a persistent feature at all stages of psychosis and implied that the existing treatment options are not effective towards alleviating the symptoms of CD (Harrow and Marengo, 1986; Andreasen and Grove; 1986; Marengo and Harrow, 1997).

## 1.7 Neural correlates of conceptual disorganization - a review of the neuroimaging literature

Numerous neuroimaging studies have sought to investigate the neural correlates of CD (more specifically, FTD) in established psychosis (schizophrenia), which have been

systematically reviewed (Sumner et al., 2018a, 2018b; Kircher et al., 2018; Cavelti et al., 2018).

Sumner et al. (2018a) reviewed studies which investigated the functional correlates of thought disorder and reported the frontal and temporal lobes, fusiform gyrus, cingulum and some subcortical structures (caudate nucleus, cerebellum) as the brain regions associated with functional activations in relation to positive thought disorders. Functions of the temporal lobe including language perception, comprehension and production, semantic information processing were related to the severity of thought disorders. Tasks of the frontal lobe related to attention and working memory were also implicated to be related to thought disorders. This review also lists studies which conducted exploratory analyses on specific regions-of-interest (ROI) in relation to negative thought disorders. A ROI study reported increased temporal activation when performing tests of executive functioning (e.g. the Wisconsin card sorting test) in relation to thought disorders. The real-world functioning deficits, or the behavioural correlates, reported in this review associated the severity of thought disorders with the production of less syntactically complex sentences and the number of pauses between words which were filled with non-word sounds.

Another review by Sumner et al. (2018b) reviews the structural correlates of thought disorder and reports heterogeneous findings with respect to measures of brain structure (e.g. gray matter volume, thickness, gyrification) and the severity of thought disorders. In both reviews, the superior temporal gyrus has been implicated (structurally and functionally) to be an important brain region associated with language processing. This review also lists studies which reported reduced gray matter volume directly related to the severity of positive and total thought disorders, and also showed a greater loss of temporal lobe volume in individuals who had recently experienced a first episode of psychosis. Some drawbacks which include the lack of studies conducting a hypothesis-driven investigation of the structural and functional correlates of thought disorders, the non-specificity of assessment scales used to measure the severity of thought disorders, as well as the non-specificity of investigations into the defining aspects of thought disorders have been implied in these reviews.

Cavelti et al. (2018) included studies which examined the association of formal thought disorder (FTD) with either the whole brain or a ROI in the language network. They separately reviewed findings from volumetric, diffusion tensor imaging, resting-state functional MRI (fMRI) and task-based fMRI studies, and reported deficits in regions of the language network (e.g. superior temporal gyrus). A few resting-state fMRI studies have associated the severity of FTD with altered functional (resting state) activity in brain regions not part of the language network such as the insula (Horn et al., 2009; Skudlarski et al., 2010) and cingulate gyrus (Sabri et al., 1997; Skudlarski et al., 2010). In contrast, a few studies have reported observations of no relation between FTD and resting state activity in the cingulate gyrus (Liemburg et al., 2012) as well as no correlation of resting state activity with the severity of FTD in subcortical brain regions such as the thalamus and basal ganglia (Sabri et al., 1997). This review demonstrates very heterogeneous findings of the association of the language network with the severity of FTD, therefore suggesting the multifaceted nature of the disorder of the form of thought processes. Methodological differences such as a distinctly different gender ratio across all studies and inconsistencies in the measurement of clinical variables (e.g. duration of illness, medication status, and severity of FTD) were reported in this review.

Kircher et al. (2018) reviewed the positive and negative, as well as the objective and subjective symptoms of FTD and discussed their genetic, structural and functional underpinnings in relation with the severity of the symptoms of FTD. The existing literature has focused on alterations in language networks in relation to the severity of FTD. However, the authors of this review argued that since language is not a specific human ability, there is a need to conduct more studies which would investigate the aspects of FTD that are related to real-world functioning abilities such as speech processing (involving the perception and generation of speech) and social cognition.

In summary, these reviews have indicated a significant focus towards the investigation of aberrations in brain regions associated with language processing (especially superior temporal gyrus (STG)) as the major structural and functional correlates of FTD (Sumner et al., 2018a, 2018b; Wensing et al., 2017). Nevertheless, null findings, as well as findings that implicate brain regions not considered a part of the language network, have also been

reported (Sumner et al., 2018a, 2018b). A notable lack of studies which directly relate network-level functional connectivity (FC) to disorganization has also been highlighted (Cavelti et al., 2018).

A limited number of resting-state fMRI (rs-fMRI) studies have investigated the network level dysconnectivity underlying the symptoms of disorganization. In a sample of patients presenting with first episode psychosis, an increased functional connectivity (FC) of the default mode network (DMN) with the insula and dorsolateral prefrontal cortex (dlPFC) was reported in relation to clinical measures (He et al., 2013). In contrast, another study reported no alterations of FC between the DMN and other resting state networks as well as no evidence of aberrant FC within the DMN (Repovs et al., 2011) in patients with established psychosis (schizophrenia). This study also reported altered FC between the frontoparietal and cerebellar networks (Repovs et al., 2011). In another study investigating the connectivities across five resting state networks (default mode network, fronto-parietal network, cingulo-opercular network, cerebellar network, salience network) in schizophrenia, reduced network-level FC was shown to be decreased between the cingulo-opercular and salience networks, fronto-parietal and cingulo-opercular networks, as well as fronto-parietal and cerebellar networks (Mamah et al., 2013). Other studies report reduced connectivity between the thalamus and postcentral gyrus (Skudlarski et al., 2010), between dorsolateral prefrontal cortex (DLPFC) and insula, Wernicke's area, sensorimotor area and frontal pole, and increased connectivity between the DLPFC and premotor cortex (Cole et al., 2011) in relation to pronounced CD or FTD. Several studies have also failed to find a relationship between the severity of disorganization and FC (Palaniyappan et al., 2013b, 2018b; Cavelti et al 2017; Kircher et al., 2018). With the exception of one study by He et al. (2013), all other studies recruited patients during a stable medicated phase of established psychosis (schizophrenia). Therefore, the neural correlates of conceptual disorganization seen during first episode psychosis is still unclear.

## 1.8 Current limitations in existing literature

One limitation in identifying the prevalence of FTD (or CD) in psychosis samples is the absence of cutoff scores and validation studies as well as the limited number of studies using more than one assessment tool to indicate the presence of FTD (Roche et al., 2015).

A second limitation is the paucity of studies explicitly relating FTD to impairments in social cognition (Kircher et al., 2018), an important component of real-world functioning (Rocca et al., 2018). A comprehensive review of neuroimaging studies in schizophrenia reveals the absence of adequate sample sizes to study the structural and functional correlates of FTD as well as a heterogeneity in assessment scales used to measure FTD (Cavelti et al., 2017). Alongside these observations, the majority of neuroimaging studies have been reported to investigate structural and functional alterations of brain regions primarily involved in auditory and language processing with few studies investigating higher-order cognitive processing (eg. social cognition, working memory and executive functioning) in FTD. The review by Cavelti et al. (2017) reveals a gap in the literature of studies that have investigated whole-brain connectivity patterns voxel-by-voxel in relation to the severity of conceptual disorganization.

The next sections review the imaging modality of functional magnetic resonance imaging (fMRI), the imaging techniques and graph theoretical measures used in this study as tools to assess the severity of psychotic symptoms.

## 1.9 Use of functional Magnetic Resonance Imaging (fMRI) as a tool to study psychosis

Patterns of brain activity in disorders such as psychosis were initially studied using animal models, post-mortem studies and examination of the concentrations of peripheral metabolites (Andreasen, 1988). However, these approaches had some inherent limitations; for example, animal models could not be used to study the distinctive cognitive or behavioural abilities observed in humans, a post-mortem investigation of brain tissue would not be able to account for effects of dynamically changing confounding variables (e.g. age, treatment with various medications, alterations in brain tissue associated with other diseases). An examination of concentrations of peripheral metabolites would not be helpful towards explaining alterations in concentrations of brain metabolites, or neurochemical processes in the brain. In summary, these techniques could not provide a

means to investigate the structural, functional, chemical, cognitive or behavioural components associated with psychosis.

It, therefore, became imperative to study changes in the brain through direct observations in living human beings. In vivo neuroimaging became a widely used tool with different techniques to study the human brain. Functional magnetic resonance imaging (fMRI) is a technique commonly used to study brain function. It uses a strong magnetic field to detect changes in blood flow patterns in the brain as a marker of brain function. fMRI is a powerful non-invasive tool used to measure changes in blood flow patterns and blood oxygenation levels associated with changes in neuronal activity either at rest or when performing a particular task. The most popular fMRI technique used to study brain activity, Blood Oxygen Level Dependent (BOLD) imaging, allows us to study hemodynamic responses to neuronal firing. This imaging technique takes advantage of the differences in magnetic properties of oxygenated and deoxygenated hemoglobin. The fMRI modality used to study patterns of brain activation in this study is resting-state fMRI.

## 1.10 Description of the imaging technique(s) used in this study

Resting-state fMRI (rs-fMRI) and structural MRI are two imaging techniques used in this study.

### *Resting-state functional magnetic resonance imaging (rs-fMRI)*

This is an in vivo non-invasive imaging technique which was first described by Biswal et al., in 1995. Rs-fMRI is used to study changes in blood flow and oxygenation patterns in the brain of an individual at rest or without the presence of any external stimulus. In other words, resting-state fMRI is used to measure the BOLD signal when the brain is not explicitly involved in performing any task/activity. During the scan, the individuals are instructed to lay inside the scanner, either with their eyes open or closed and asked to not think of anything in particular. Rs-fMRI is helpful for scanning participants with severe psychiatric conditions (e.g. psychosis), who might experience difficulties in performing tasks within the scanner environment.

### *Structural magnetic resonance imaging*

This is a non-invasive imaging technique which is used to examine the anatomy and pathology of the brain. Structural MRI provides qualitative and quantitative information about the shape, size and integrity of gray and white matter structures in the brain. It also provides an anatomical reference for the visualization of activation patterns and regions of interest to extract functional signal information.

### 1.10.1 Imaging sequences: rs-fMRI and structural MRI

The properties of magnetic resonance imaging sequences are based on the random orientation or anisotropy of water molecules when a strong, uniform, external magnetic field is applied to different types of brain tissue. The anisotropy of water molecules is influenced by the application of an external radio frequency (RF) pulse to the magnetic field. Different image sequences are obtained by varying the sequences of RF pulses applied to the field and collected from the emitted signals. During image acquisition, the time interval between the application of two successive RF pulses is known as repetition time (TR) and the time interval between the application of an RF pulse and receipt of the echo signal is known as echo time (TE).

‘Relaxation time’ is a measure which can help differentiate between different tissue types alongside measures of TR and TE. In magnetic resonance imaging, ‘relaxation’ can be defined as a measure of change in emitted signal over time. Tissues can be classified based on two types of relaxations- T1 (longitudinal) and T2 (transverse). The time constant which determines the rate at which excited protons return to equilibrium, or conversely, the time taken for spinning protons to lose their ‘spin’ momentum and align with the magnetic field is known as T1. The time constant at which excited protons go out of phase with each other, or alternatively, the time taken by the excited protons to lose phase coherence and spin orthogonal to the magnetic field is known as T2. The time constants TR and TE are used to characterize the T1 and T2 properties of the tissue respectively.

Resting state functional magnetic resonance imaging is characterized by T2\*-weighted images. T2\* weighting is obtained by both the T2 signal as well as inhomogeneities of the

external magnetic field. In our acquisition protocol, the TR of rs-fMRI data is 1000 milliseconds and the TE is 20 milliseconds. Structural magnetic resonance imaging is characterized by T1-weighted images. In our acquisition protocol, the TR of structural MRI data is 6000 milliseconds and the TE is 2.83 milliseconds.

## 1.11 Graph theoretical measures and the theory of ‘dysconnection’ in psychosis

Graph theory is a branch of mathematics which is used to define a real-world complex system in the form of nodes (vertices of the graph) and connections between the nodes (edges of the graph). It has been widely used to characterize structural and functional brain networks in terms of graph metrics namely, nodes (specialized brain regions) and edges (axons, dendrites, and synaptic terminals) (Bullmore & Sporns, 2009). Furthermore, graph theory has been successful in demonstrating aberrant patterns of structural and functional network connectivities in medicated patients with established psychosis (chronic schizophrenia) (Zalesky et al., 2011; Palaniyappan & Liddle, 2014; Yu et al., 2015; Cheng et al., 2015; Cao et al., 2016; Kambeitz et al., 2016; Palaniyappan et al., 2018a). Therefore, measures of graph theory are useful to characterize the the theory of ‘dysconnection’ (Friston & Frith, 1995) in relation to brain networks.

### 1.11.1 The ‘dysconnection’ hypothesis

Wernicke’s hypothesis of ‘sejunktion’ suggested that an aberrant shunting of neural processes occurring in psychosis resulted in a disruption of interconnections and abnormal functionalities in distributed neural systems (Ungvari, 1993). Following this, the concept of ‘splitting’ or ‘disintegration’ of different psychological domains in established psychosis was proposed by Bleuler in 1911, based on Janet’s concepts of ‘association’ and ‘dissociation’ (Moskowitz, 2006). In 1995, Friston and Frith united the concepts of ‘sejunktion’ and ‘disintegration’ to put forward the ‘dysconnection hypothesis’ which suggested that the core symptoms of psychosis (schizophrenia) result in an abnormal functional integration in distributed brain networks (Friston & Frith, 1995). Stephan et al. in 2009 proposed an alternate pathophysiological framework of schizophrenia to suggest that the underlying abnormal functional integration of distributed brain networks explains

the characteristic core symptoms and associated cognitive impairments in schizophrenia (Stephan et al., 2009).

### 1.11.2 Description of graph theoretical measures used in this study

The graph theoretical measures used in this study to assess the presence and severity of disorganization in psychosis are degree centrality (quantitative) and hubness (qualitative).

Degree centrality (DC) is a quantitative graph theoretical metric which was first introduced by Buckner et al., 2009. It is defined as the number of voxels across the brain that are strongly correlated with the target voxel (Buckner et al., 2009). This metric measures the local network connectivity by accounting for the number of direct extrinsic or intrinsic connections (edges) one node has to all other nodes in a distributed brain network. A node with high DC, therefore, has a large number of direct connections to other nodes in the network.

Hubness is a qualitative graph theoretical metric used to quantify the characteristics of nodes or brain regions with high DC in a brain network. Nodes with high DC have high hubness (or hub-like properties) and are crucial to efficient communication. On the other hand, nodes with low DC are regions through which information flow occurs but are not important for efficient communication. Increased hubness of a node would indicate an increase in its hub-like properties and thus its emergence as a crucial network node for information exchange. In contrast, reduced hubness of a node would indicate a reduction in hub-like properties of a brain region, therefore lowering its importance in the network.

These two complementary graph metrics measure the number of connections each brain region has to other brain regions. These graph metrics would help characterize aberrant connectivity patterns which occur in distributed brain regions as a result of the underlying symptoms of disorganization in first episode psychosis. Such a characterization would help study the theory of 'dysconnection' in an acutely psychotic sample and may also provide insights as to whether the symptoms are a result of the functional aberrations (or vice-versa).

### 1.11.3 The methodological approach used in this study to detect altered functional connectivity with respect to conceptual disorganization

Without making any a priori assumptions about the brain regions implicated in acute disorganization, a graph theoretical measure known as degree centrality (DC) (first introduced by Buckner et al., 2009) was used to characterize differences in local network connectivity between the two groups across the whole brain. We undertook a whole brain voxel wise search to locate brain regions showing aberrant connectivity in relation to the presence of psychosis as well as the severity of disorganization. A correlation threshold of  $r > 0.25$  (Buckner et al., 2009; Zuo et al., 2012; Yan et al., 2013a, b) was used to generate an undirected adjacency matrix to identify the brain voxels which were strongly connected to other brain voxels. To establish the specificity of our findings on the symptom of conceptual disorganization, we studied the effects of other positive and negative symptoms of psychosis in relation to the observed results.

#### 1.11.3.1 Influence of thresholding parameters

While computing topological properties such as centrality based on graph theory to study brain connectomes, a limited number of brain regions are usually selected as nodes of interest, and sparse connectivity matrices are obtained to delineate the networks of interest. The 2 commonly used approaches to generate sparse matrices are (1) the use of an absolute edge-defining threshold (e.g. edges with functional connectivity value above 0.25 are retained as in Buckner et al., 2009) or (2) using a fixed edge density threshold (e.g. 30% of all possible edges are retained in the matrices). The use of an absolute edge defining threshold can result in various sparsity values across different individuals (or groups). As several topological metrics depend on the degree of sparsity (Tewarie et al., 2014), the resulting differences may indeed be due to variations in the number of edges rather than true differences in the network topology. Proportional thresholding using several values of fixed edge density obviates this problem (e.g. Bassett et al., 2008). But when using this approach, if systematic differences in the global strength of connectivity exist between two groups of interest, this can result in noisy and spurious edges with low connectional

strength being included in one group and not in the other. Again, this could lead to an apparent group difference in topological metrics, with a shift towards randomness in the group with weaker overall connectivity (van den Heuvel 2017; Vasa et al., 2018). Our primary interest was not in deriving the topological architecture of functional connectivity. Instead, we were focused on deriving a single score for each voxel that best represented the overall (voxelwise) functional connectivity required to characterize hubs. As a result, we used Buckner's approach in this study. Our previous use of this approach resulted in highly reproducible hubs across different brain states (rest, 0,1, and 2 back task performance) (Palaniyappan & Liddle 2014).

## 1.12 Influence of assessment procedure used to measure disorganization

Disorganization and the related construct of FTD are both multidimensional constructs, with variations along the axes of subjectivity, positive-negative speech productivity, as well as illness stage related (i.e. acute vs chronic) differences. As recommended by recent comprehensive reviews in this field (Cavelti et al., 2018; Kircher et al., 2018; Sumner et al., 2018), we assessed both a positive (P2 of PANSS) and a negative (N6 of PANSS) feature of FTD. In addition, we also corroborated the presence of disorganization using complementary clinical definitions (YMRS scale items 6 and 7). Nevertheless, our results cannot be taken to represent the neural basis of FTD as such, as we lacked instruments that comprehensively quantify the various aspects of FTD (Kircher et al., 2018; Strik et al., 2010).

## 1.13 Aims and Hypotheses

The aim of this study was to investigate whole brain alterations of functional connectivity in patients presenting with first-episode psychosis in comparison with healthy controls. A second aim was to relate the symptoms of disorganization to these functional connectivity alterations.

Our hypothesis is that in association with the symptoms of disorganization, there is a reduction in hubness (measured using degree centrality) of major brain areas in patients presenting with drug-naïve first-episode psychosis in comparison to healthy controls.

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## Chapter 2: *Manuscript*

### 2 Title: Conceptual disorganization and redistribution of resting state cortical hubs in untreated first episode psychosis: A 7T study

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#### 2.3 Abstract

*Background:*

Network level dysconnectivity has been studied in positive and negative symptoms of schizophrenia. Conceptual disorganization (CD) is a symptom which predicts impaired real-world functioning. Systematic reviews have reported aberrant connectivity in formal thought disorder, a construct related to CD. However, no studies have investigated whole-brain functional correlates of CD in psychosis. We sought to investigate brain regions

explaining the severity of CD in patients with first-episode psychosis (FEPs) compared with healthy controls (HCs).

*Methods:*

We computed whole-brain binarized degree centrality maps of 31 FEPs, 25 HCs and characterized the patterns of network connectivity in the two groups. In FEPs, we related these findings to the severity of CD. We also studied the effect of positive and negative symptoms on altered network connectivity.

*Results:*

Compared to HCs, the FEPs showed reduced hubness of a cluster located in the right superior temporal gyrus (rSTG). In patients exhibiting high CD, increased hubness of a medial superior parietal (mSPL) cluster was observed, compared to patients exhibiting low CD. These two regions were strongly correlated with CD scores but not with other symptom scores.

*Discussion:*

Our observations are congruent with previous findings of reduced but not increased hubness. We observed increased hubness of mSPL suggesting that cortical reorganization occurs to provide alternate routes for information transfer.

*Conclusion:*

These findings provide insight into the underlying neural processes mediating the presentation of symptoms in untreated FEP. A longitudinal tracking of the symptom course will be useful to assess the mechanisms underlying these compensatory changes.

## 2.4 Keywords

conceptual disorganization, first-episode psychosis, resting-state fMRI, graph theory, cortical reorganization

## 2.5 Introduction

Disorganization is one of the three distinct syndromes of schizophrenia (Bilder et al., 1985; Kulhara et al., 1986; Liddle, 1987; Andreasen et al., 1995), defined collectively as the impairment of the form of thought processes (conceptual disorganization) and bizarre actions (behavioural disorganization). Conceptual disorganization (CD), in particular, is comprised of difficulties in the goal-directed sequencing of thoughts that manifest as circumstantial, illogical or tangential speech or weakened goal of thinking (loose associations) (Kay et al., 1987). CD has been shown to be tightly linked to real-world functioning (Bellack et al., 1994; Galderisi et al., 2014; Rocca et al., 2018). Conceptual disorganization is also referred to as ‘formal thought disorder (FTD)’, though the latter is often measured using specific instruments that focus on testing aspects of speech rather than the clinical interpretation of disorganization. While the construct of FTD encompasses both positive (e.g. illogical, tangential, loosened speech) as well as negative (e.g. poverty of speech, reduced content of speech) FTD, the clinical construct of CD refers only to positive aspects of FTD.

CD is seen in both acute and chronic stages of established psychosis (schizophrenia) (Feigenson et al., 2014), with some indication that the pathophysiology of persistent CD may be distinct from the acute CD seen during an active psychotic episode (Breier and Berg, 1999). For example, the acute CD resolves in many patients over time (Andreasen, 1979; Harrow and Marengo, 1986; Harrow, Marengo & McDonald, 1986; Harvey, Earle-Boyle & Wielgus et al., 1984), and often covaries with the severity of positive symptoms such as delusions and hallucinations, while the CD seen in chronic stages often emerge as a distinct subtype, with more negative features of FTD being noted (Roche et al., 2014). The persistence of CD despite treatment in longitudinal cohorts has also led to the suggestion that existing treatments are not fully effective in alleviating the degree of disorganization in patients with psychosis (Harrow and Marengo, 1986; Andreasen and Grove; 1986; Marengo and Harrow, 1997).

A large body of neuroimaging literature has attempted to parse the brain regions implicated in the thought disorders of schizophrenia (Kircher et al., 2018), with several comprehensive systematic reviews (Roche et al., 2014; Kircher et al., 2018; Cavelti et al.,

2018) providing an excellent overview of the reported brain correlates of conceptual disorganization (more specifically, FTD). These reviews indicate that a large number of studies have focussed explicitly on aberrations in language processing brain regions (especially superior temporal gyrus) as the major structural and functional underpinnings of FTD (Sumner et al., 2018; Wensing et al., 2017). Nevertheless, null findings as well as findings that implicate brain regions that are not considered to be a part of the language network are also reported (Sumner et al., 2018). A notable lack of studies directly relating network-level functional connectivity to disorganization has been highlighted (Cavelti et al., 2018).

A limited number of resting-state fMRI (rs-fMRI) studies have investigated the network level dysconnectivity underlying disorganization. These studies report reduced connectivity between thalamus and postcentral gyrus (Skudlarski et al., 2010), between the frontoparietal and cerebellar networks (Repovs et al., 2011), between dorsolateral prefrontal cortex (DLPFC) and insula, Wernicke's area, sensorimotor area and frontal pole, and increased connectivity between DLPFC and premotor cortex (Cole et al., 2011) in relation to pronounced disorganization or FTD. Taken together, dysconnectivity of several brain regions outside of the traditional language network appears to contribute to the severity of disorganization. Several studies have also failed to find a relationship between severity of disorganization and functional connectivity (Palaniyappan et al., 2013b, 2018a; Kircher et al., 2018; Cavelti et al 2017). All of these studies have been conducted on established cases of schizophrenia, with patients recruited during a stable medicated phase of illness. Thus, the neural basis of acute disorganization seen during first episode psychosis is still unclear. Furthermore, to our knowledge, there have been no studies to date that investigate voxel-by-voxel whole-brain connectivity in relation to disorganization.

In the current study, we quantified acute conceptual disorganization from a sample of 38 untreated patients with first-episode psychosis (FEP) and 31 age-matched healthy controls. We acquired rs-fMRI scans from an ultra-high field 7-tesla MRI scanner. Without making any a priori assumptions about the brain regions implicated in acute disorganization, we first undertook a whole brain, voxel wise search to locate brain regions showing aberrant

connectivity in relation to the presence of psychosis as well as the severity of disorganization. To establish the specificity of our findings to the symptom of conceptual disorganization, we studied the effect of other positive and negative symptoms of psychosis in relation to the observed results.

## 2.6 Materials and Methods

### 2.6.1 Participants

The sample consisted of 51 consecutive new referrals to the PEPP (Prevention and Early Intervention for Psychosis Program) at London Health Sciences Centre, London, Ontario, Canada between April 2017 and July 2018. The PEPP program uses an assertive case-management model to provide assessment and treatment to individuals 16-39 years old experiencing FEP. All potential study participants provided written, informed consent prior to participation as per the approval provided by the Western University Health Sciences Research Ethics Board, London, Ontario.

Inclusion criteria for study participation were as follows: individuals experiencing a first episode of psychosis and having received antipsychotic treatment for less than 14 days in their lifetime. Both inpatients and outpatients were eligible to participate if they were able provide informed consent and safely participate in the MRI protocol. All participants received a consensus diagnosis from 3 psychiatrists (LP/KD and the primary treatment provider) after approximately 6 months on the basis of the best estimate procedure (as described in Leckman et al., 1982) and the Structured Clinical Interview for DSM-5 (APA, 2013). Following the 6-month consensus diagnosis, participants meeting criteria for bipolar disorder with psychotic features, major depressive disorder with psychotic features, or suspected drug-induced psychoses were excluded from further analyses. Care was provided as usual to the study participants through their psychiatrist and other allied health members with the PEPP program. Antipsychotic medications were chosen by the treating psychiatrist in collaboration with the patient and/or their substitute decision-maker. Individuals were offered the option of treatment with a long-acting injectable at the earliest

opportunity (Remington et al., 2017) in accordance with current national guidelines for the treatment of FEP.

Recruitment of healthy control subjects ( $n = 31$ ) was carried out through posters which advertised the opportunity to participate in a neuroimaging study to track the outcomes of FEP. Healthy control subjects had no personal history of mental illness and no family history of psychotic disorders. Group matching with the FEP cohort for age, gender and parental education was maintained.

Exclusion criteria for both the FEP and healthy control groups involved meeting criteria for a substance use disorder in the past year according to DSM-5 criteria (DSM-5; APA, 2013), having a history of a major head injury (leading to a significant period of unconsciousness or seizures), having a significant, uncontrolled medical illness, or having any contraindications to undergoing MRI.

### 2.6.2 Clinical and cognitive assessments

The severity of symptoms in patients was assessed using the 8-item Positive and Negative Syndrome Scale (PANSS-8) which measures the severity of positive and negative symptoms. We also used the Social and Occupational Functioning Assessment Scale (SOFAS) to assess the overall level of functioning (Morosini et al., 2000). We also used a modified digit symbol substitution task (DSST) to quantify processing speed, a cognitive function that shows the most prominent reduction among patients with psychosis (Dickinson et al., 2008). The written and oral items on the DSST were scored separately, and the mean scores from these items were used for assessment as in our prior study (Palaniyappan et al., 2013a).

Scores from the PANSS-8 scale were grouped into a positive component (P1, P3 and G9 measuring ‘delusions’, ‘hallucinations’ and ‘unusual thought content’ respectively), a negative component (N1, N4 and N6 measuring ‘blunted affect’, ‘passive/apathetic social withdrawal’ and ‘lack of spontaneity & flow of conversation’ respectively) and P2 measuring ‘conceptual disorganization’. These 8 items were chosen as they are the most

indicative of the achievement of clinical remission when patients receive treatment (Andreasen et al., 2005) scores. The PANSS-8 was applied by one of the 2 research psychiatrists (LP or KD) on the same week of the MRI acquisition, prior to the patients receiving clinically adequate treatment (i.e. at first contact on presentation). In addition, we also quantified the severity of 2 domains of negative symptoms using Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011) and overall illness severity using Clinical Global Impression (CGI) (Guy, 1976).

Patients who scored 1, 2 or 3 points on individual PANSS items were categorized to have low severity of the specific symptom (e.g. low P2), compared to those who scored 4, 5, 6 or 7 (high P2). We chose this cut-off to distinguish those who have clinically severe vs. minimal symptoms recommended by the Remission Working Group (Andreasen et al., 2005). This cut-off has also been recently employed to distinguish patients with or without formal thought disorder and language dysfunction (Çokal et al., 2018).

As different antipsychotics were prescribed, we used WHO's algorithm for defined daily doses (DDD) for antipsychotic medications (WHO, 2013) to obtain a common unit of exposure. DDD refers to a specific amount i.e. a ratio unit of the defined daily dose whose absolute milligram units varies among the different medications.

Measure	Group			Group Comparison	
	High P2	Low P2	Healthy controls	F / T / $\chi^2$	p – value
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)		
<i>Subjects included in the final analysis</i>					
<b>Demographic information</b>					
Number of subjects	12	26	31		
Age (years)	21 (2.80)	23.15 (5.04)	21.61 (3.26)	1.61	0.21
Gender (M/F) <sup>^</sup>	11 / 1	21 / 5	19 / 12	5.02	0.08
Exposure to antipsychotic medication (days)	2.57 (3.55)	5.53 (4.48)	-	1.69	0.21
Duration of untreated illness (days)	207 (186)	343 (579)	-	2.36	0.13
Total DDD of antipsychotics	1.04 (1.79)	2.91 (2.95)	-	2.26	0.15
Diagnosis (SCZ / Other psychoses) <sup>^</sup>	8 / 4	21 / 5	-	0.90	0.34
National Statistics Socio-Economic Classification score	3.67 (1.22)	3.47 (1.30)	3.20 (1.42)	0.50	0.61
<b>Clinical and Cognitive assessments</b>					
<i>PANSS-8</i>					
Conceptual disorganization (P2) <sup>†</sup>	4.5 (0.67)	1.73 (0.92)	-		< 0.001
Lack of spontaneity & flow of conversation (N6) <sup>†</sup>	1.92 (0.996)	2.04 (1.31)	-		0.96
Total positive component (P1 + P3 + G9)	14.10 (2.02)	13.00 (2.56)	-	1.20	0.24
Total negative component (N1 + N4)	5.80 (3.26)	5.61 (3.22)	-	0.16	0.88
<i>Thought and Language Index (TLI)</i>					
Impoverishment in thinking	0.26 (0.26)	0.10 (0.16)	0.02 (0.06)	11.85	< 0.001 <sup>a</sup>
Disorganization in speech	0.36 (0.41)	0.22 (0.21)	0.05 (0.08)	9.28	< 0.001 <sup>a</sup>
<i>YMRS</i>					
Speech rate & amount (YMRS 6) <sup>†</sup>	0.75 (1.49)	0 (0)	-		0.04
Language / Thought disorder (YMRS 7) <sup>†</sup>	2.88 (1.81)	0.75 (1.41)	-		< 0.001
SOFAS	37.50 (8.81)	41.83 (13.69)	79.96 (4.77)	109.17	< 0.001 <sup>b</sup>
DSST (Mean)	53.00 (17.10)	53.27 (12.90)	68.63 (10.93)	12.26	< 0.001 <sup>b</sup>
<sup>†</sup> Mann Whitney U-test	<sup>^</sup> chi-square test	S.D. = Standard deviation	DDD = Defined daily dose of antipsychotics	<sup>b</sup> High P2 = Low P2 < HC	
<sup>a</sup> High P2 > Low P2 > HC	High P2: Patients with high conceptual disorganization		Low P2: Patients with low conceptual disorganization		

**Table 1** Demographic and clinical characteristic of the sample included for analysis in the study.

Measure	Group			Group Comparison	
	High P2	Low P2	Healthy controls	F / T / $\chi^2$	p - value
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)		
<i>Subjects excluded from the final analysis</i>					
<b>Demographic information</b>					
Number of subjects	9	4	0		
Age (years)	22.23 (3.64)	21.75 (4.57)	-	0.30	0.77
Gender (M/F) <sup>^</sup>	8 / 1	2 / 2	-	2.36	0.13
Exposure to antipsychotic medication (days)	n.a.	n.a.	-		
Duration of untreated illness (days)	551 (787.85)	212.5 (147)	-	0.83	0.42
Total DDD of antipsychotics	n.a.	n.a.	-		
Diagnosis (SCZ / Other psychoses) <sup>^</sup>	6 / 3	1 / 1 <sup>‡</sup>	-	0.19	0.67
National Statistics Socio-Economic Classification score	3.11 (1.45)	2.33 (1.53)	-	0.80	0.45
<b>Clinical and Cognitive assessments</b>					
<i>PANSS-8</i>					
Conceptual disorganization (P2) <sup>†</sup>	4.56 (0.527)	2.00 (1.16)	-		0.003
Lack of spontaneity & flow of conversation (N6) <sup>†</sup>	1.56 (0.882)	1.75 (0.957)	-		0.71
Total positive component (P1 + P3 + G9)	13.22 (2.54)	10.75 (0.96)	-	1.85	0.09
Total negative component (N1 + N4)	3.56 (2.83)	5.00 (2.16)	-	0.90	0.39
<i>Thought and Language Index (TLI)</i>					
Impoverishment in thinking	0.08 (0.14)	0.21 (0.31)	-	0.589	0.46
Disorganization in speech	0.03 (0.05)	0.70 (0.71)	-	6.397	0.03
<i>YMRS</i>					
Speech rate & amount (YMRS 6) <sup>†</sup>	1.21 (1.72)	0 (0)	-		< 0.001
Language / Thought disorder (YMRS 7) <sup>†</sup>	2.79 (1.27)	0.73 (1.85)	-		< 0.001
SOFAS	35.22 (10.39)	46.50 (11.21)	-	1.77	0.11
DSST (Mean)	46.39 (9.97)	57.25 (2.90)	-	2.09	0.06
<sup>^</sup> chi-square test		<sup>†</sup> Mann Whitney U-test		S.D. = Standard deviation	
DDD = Defined daily dose of antipsychotics		<sup>‡</sup> data unavailable for other 2 subjects		n.a. = not available for dropout subjects	
High P2: Patients with high conceptual disorganization			Low P2: Patients with low conceptual disorganization		

**Table 2** Demographic and clinical characteristics of the sample excluded from analysis in the study.

### 2.6.3 MRI acquisition

All magnetic resonance (MR) images were acquired on a 7.0 T Siemens (Erlangen, Germany) Magnetom magnetic resonance imaging (MRI) scanner using a 32-channel head coil at the Centre for Functional and Metabolic Mapping (CFMM), Robarts Research Institute, Western University.

#### Functional (resting-state) MRI data (rs-fMRI)

A T2\*-weighted 2D gradient echo planar imaging (EPI) sequence with 360 volumes [acquisition time = 6 min; repetition time (TR) = 1000 ms; echo time (TE) = 20 ms; flip angle = 30°; FOV (read, phase) = 208 mm, 100%; number of slices = 63; slice thickness = 2 mm] was collected. Subjects were instructed to lay still inside the scanner with their eyes open for the duration of the scan and not to think of anything in particular. Foam pads were used to minimize subject head motion, and headphones were used to reduce scanner noise. Dummy scans were acquired prior to the acquisition of resting-state functional volumes to allow for the stabilization of both the signal and magnetic field.

#### Structural MRI data

High-resolution T1-weighted sequences were collected for co-registration with the EPI and had the following parameters: acquisition time = 9 min 38 s; TR = 6000 ms; TE = 2.83 ms; flip angles = 4°, 5°; FOV (read, phase) = 240 mm, 100%; number of slices = 63; slice thickness = 0.75 mm.

### 2.6.4 Data preprocessing

All steps of data processing and analysis are displayed in Figure 1.

Preprocessing of rs-fMRI data was performed using the Data Processing Assistant for Resting-State fMRI Advanced toolbox (DPARSFA, Yan and Zang 2010,

<http://rfmri.org/DPARSF>), which is based on the Statistical Parametric Mapping software (SPM, <http://www.fil.ion.ucl.ac.uk/spm>, version 12) and the toolbox for Data Processing & Analysis of Brain Imaging (DPABI, Yan et al., 2016, <http://rfmri.org/DPABI>).

All 360 functional volumes (rs-fMRI) acquired from each subject were corrected for differences in slice acquisition times, following which images were spatially realigned to the mean image of the dataset to correct for small movements that occurred between scans. Individual T1-weighted structural images were co-registered to the mean of the realigned EPI images, followed by segmentation into gray matter, white matter, and cerebrospinal fluid (Ashburner and Friston, 2005) tissue classes. The “Diffeomorphic Anatomical Registration using Exponentiated Lie algebra” or DARTEL toolbox (Ashburner, 2007) used the information from the previous step to generate tissue class images which were rigidly transformed and in close alignment with SPM tissue probability maps.

Rs-fMRI signal measures have been shown to be highly sensitive to micro-scale head motions (Yan et al., 2013a). We derived the 24 motion parameters (Friston et al., 1996) (6 head motion parameters [t], 6 head motion parameters at the previous time point [t-1], and the squared values of these 12 measures), and regressed the variance in BOLD signal amplitude that related to these motion parameters from the realigned data, before further processing.

To control for the effects of confounding factors, linear and quadratic trends in the data as well as the signals from the white matter and cerebrospinal fluid were removed from the data with linear regression (Yan et al., 2013b). Following temporal filtering using a band-pass filter (0.01-0.1 Hz), linear detrending and standardization procedures were performed on the EPI images. The head motion ‘scrubbing’ routine in DPARSFA was used to correct for framewise displacement (FD) motion artifacts using the ‘nearest neighbours’ interpolation method (see Iwabuchi & Palaniyappan, 2017). For each subject, we estimated the mean FD in mm, averaged across 360 volumes to estimate the overall degree of motion during the acquisition (Power et al., 2012, 2014). This was then compared between groups to investigate if systematic differences in head motion influenced the results reported.

We excluded 13 subjects due to motion during acquisition (n=5), failure of quality check during preprocessing (n=5), experiencing anxiety inside the scanner (n=2), not resting during the scan (n=1) (13 FEPs, 0 HCs). The excluded subjects did not differ from the patients who were included in the final sample in terms of age, gender and PANSS-8 total, DSST, NSSEC, SOFAS scores (all  $p > 0.06$ ) (Table 2), except for head motion which was higher in the excluded group ( $p < 0.001$ ).

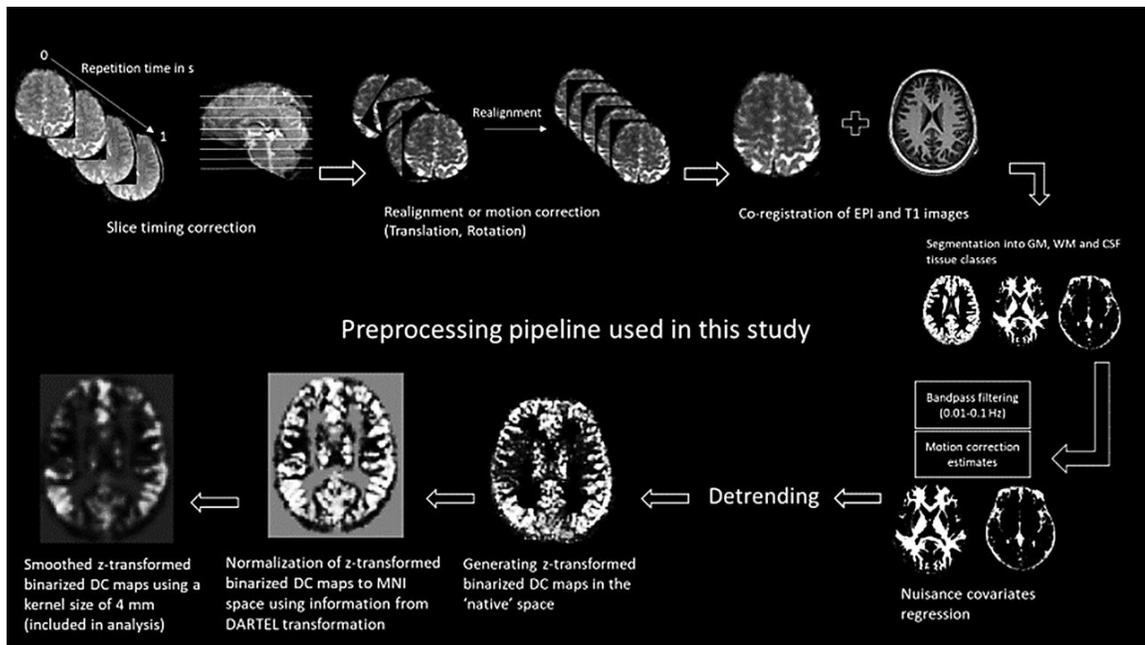
### 2.6.5 Computing degree centrality maps

To quantify the whole brain connectivity of each voxel to the rest of the brain, we employed the metric of degree centrality which was first introduced by Buckner et al., 2009. The number of connections each voxel has with every other voxel in the brain above a certain threshold ( $r = 0.25$  in this case), determines the degree centrality (DC) of that voxel. We restricted our voxel-wise analyses of degree centrality (DC) to a predefined gray matter mask to control for correlation estimates with non-gray matter voxels. This gray matter tissue probability template, released as a part of the tissue priors in SPM12, was resliced using the ‘Utilities’ function provided by the DPARSFA software to match the dimensions (104 x 104 x 63) of the acquired functional images. The gray matter mask was warped into individual space using DARTEL information to compute DC maps in the ‘native’ space for each subject.

Individual voxel-wise network centrality maps were generated within the study gray matter mask by subjecting the preprocessed functional runs to a time-series correlation analysis conducted for all voxels over the whole brain. The time-series of each voxel within the gray matter mask was correlated with the time-series of every other voxel, which resulted in a time-series correlation matrix. A correlation threshold of  $r > 0.25$  (Buckner et al., 2009; Zuo et al., 2012; Yan et al., 2013a, b) was used to generate an undirected adjacency matrix. We computed both binarized DC (bDC - the number of edges in the binarized adjacency matrix, thresholded at  $r = 0.25$ ) and the weighted DC (wDC - the sum of the weights of all pairwise connections for each voxel (Zuo et al., 2012)). The individual-level voxel-wise bDC and wDC maps were converted into respective z-score

maps by subtracting the mean DC across the entire brain and dividing by the standard deviation of the whole-brain DC (Zuo et al., 2012; Yan et al., 2013b). The resulting maps were then registered into MNI space with dimensions of isotropic 3 mm<sup>3</sup> cubic voxels using the transformation information acquired from DARTEL. A smoothing kernel of 4 mm full-width at half-maximum was applied after registration to enable parametric mapping.

As the one-sample and group comparison contrasts for both wDC and bDC were very similar to each other, we only report bDC results in the following section. The wDC maps for primary analysis (HC vs FEP comparison) are shown in Appendix 1).



**Figure 1** Steps of preprocessing performed in this study, including slice timing correction, realignment, coregistration to structural image, segmentation into GM, WM and CSF tissue classes, nuisance covariates regression, filtering, removing linear trends from data (detrending), computing DC maps in the ‘native’ space, normalization to MNI template using DARTEL information, smoothing.

## 2.7 Statistical analysis

### 2.7.1.1 Contrasts

We were primarily interested in 2 contrasts. First, to locate brain regions with aberrant connectivity in relation to FEP, we compared all FEP subjects with control subjects. Second, to locate brain regions with aberrant connectivity in relation to CD, we compared high P2 with low P2 subjects. In order to interpret the specific region-to-region functional connections affected by aberrant bDC, we used a seed-based functional connectivity approach (6 mm sphere around the centre of mass of the cluster) and studied the relationship between time series of BOLD signals of the seed and the rest of the brain within the FEP group.

### 2.7.1.2 Correction for multiple testing

For all statistical analyses in this study, the threshold for significance was set after correction for multiple testing using a familywise error correction procedure (Nichols and Hayasaka, 2013). A conservative cluster inclusion threshold of  $p < 0.001$  was used to define the clusters (Woo et al., 2014), with a cluster-level significance set at family-wise error (FWE) corrected  $p < 0.05$ . Given the limitations of clusterwise procedures when making localised spatial inferences, we primarily interpret the location of the centre of mass of the identified clusters, and not the individual voxel peaks. The nomenclature used in AAL atlas (Tzourio-Mazoyer et al., 2002) was used to label the significant clusters. As gender was not balanced between patients and controls in the final sample, gender was used as a covariate in all group contrasts.

### 2.7.1.3 Specificity of findings to P2 scores

Firstly, to demonstrate that the binary split based on a cut-off value does not spuriously result in apparent group differences, we used Spearman's correlation to relate the eigenvariate of the cluster showing bDC changes in high vs low symptom severity

comparisons to the individual symptom score. Next, to investigate if the findings are specific to P2 as a symptom and not to other symptoms of psychosis, we first compared the low and high P2 groups on the distributions of all individual symptom scores (namely, N6 - the equivalent of negative FTD, G5, positive symptoms (P1, P3, G9), as well as negative symptoms (N1, N4) of PANSS-8). We also investigated differences in the DSST scores, SOFAS, BNSS between the low P2 and high P2 groups. For the clinical features that differed between the two P2-based groups, we repeated the low vs. high severity between groups analysis of bDC maps.

## 2.8 Results

### 2.8.1 Demographic and clinical characteristics

All patients were acutely psychotic, minimally treated and had significant social and occupational dysfunction at the time of scanning. The average duration of illness (including prodrome) was 302 days (S.D. = 495 days), with the mean number of days of exposure to antipsychotic medication being < 4 days at the time of scanning.

The demographic and clinical characteristics of the sample are presented in Table 1. The two patient groups did not differ from HCs in terms of age, gender and socio-economic status. The two patient groups did not differ in terms of age, gender, socio-economic status, duration of untreated illness in days, exposure to antipsychotic medication in days, total daily dose of antipsychotic medication and the number of patients with schizophrenia in either group (diagnosed 6 months after the initial presentation). Across the three groups, we observed a significant difference for the SOFAS and DSST (mean) scores, confirmed by an ANOVA.

### 2.8.2 Effect of psychosis on bDC

Two sample t-tests of bDC between the two groups (FEP, HC) revealed a significant reduction in hubness of the right superior temporal gyrus (STG), right insula and right Heschl's gyrus in patients with FEP compared to HCs. The group differences are

shown in Table 3 and Figure 2 (a). No significant increases in hubness were observed in the patient group compared to HCs.

We also performed a two sample t-test of wDC between the two groups and observed the same brain regions showing differences in the two groups (Appendix 1).

Cluster information		Peak voxel statistics				
Brain regions included in cluster (AAL labels)	Cluster size	Peak MNI coordinates			T- value	p-value (cFWE corrected)
		x	y	z		
<b>FEP &lt; HC</b>						
<i>STG/Insula cluster</i>	148	48	-9	3	5.00	0.001
Temporal_Sup_R	75					
Insula_R	46					
Heschl_R	22					
<b>FEP &gt; HC</b>						
Not significant						
cFWE = cluster FWE	MNI = Montreal Neurological Institute	FEP = First episode psychosis	HC = Healthy controls			

**Table 3** Brain regions showing reduced hubness in the FEP (n = 38) group compared to HCs (n = 31).

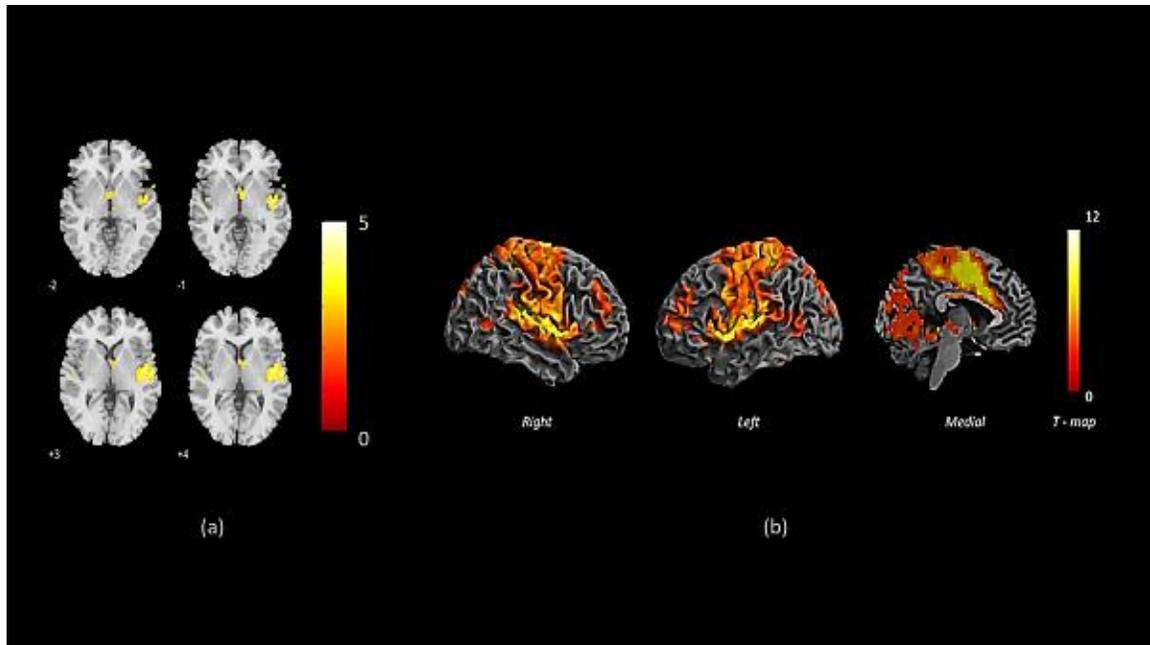
### 2.8.3 Functional connectivity of STG/insula cluster with the rest of the brain

In seed-based FC within the entire FEP group, we noted that the right STG/insula cluster showed significant functional connectivity with a set of distributed brain regions, including bilateral insula, middle cingulate region, SMA, as well as clusters in bilateral thalamus, bilateral calcarine and lingual regions extending to cerebellum (lobules 4, 5 and 6), and two clusters located at the left and right middle frontal gyrus. This indicates that the right

STG/insula cluster belongs to a distributed network of other highly connected hub regions of the salience network as well as executive network (Table 4 and Figure 2 (b)). [Also see the Appendix 2 for the meta-analytic functional connectivity data from Neurosynth database]. We did not find any significant differences in the functional connectivity between patients and control subjects on a two sample t test, indicating that the reduced hubness of the right STG/insula cluster in psychosis is not driven by any specific network level reductions in connectivity.

Cluster information		Peak voxel statistics				
Brain regions included in cluster (AAL labels)	Cluster size	Peak MNI coordinates			T-value	p-value (cFWE corrected)
		x	y	z		
<i>STG/Insula cluster</i>	10298	51	-6	3	13.23	< 0.001
Postcentral_R/L	739					
Temporal_Sup_R/L	597					
Insula_R/L	376					
Precentral_R/L	563					
Paracentral_Lobule_R/L	241					
Supp_Motor_Area_R/L	384					
<i>Thalamus cluster</i>	307	-12	-21	3	9.72	< 0.001
<i>Cerebellum cluster</i>	447	-33	-24	3	8.02	< 0.001
Calcarine_R/L	333					
Cerebellum_4_5_R/L	232					
Cerebellum_6_R/L	210					
Lingual_R/L	202					
<i>Left middle frontal gyrus cluster</i>	344	-30	33	33	8.41	< 0.001
<i>Right middle frontal gyrus cluster</i>	194	39	51	15	7.59	< 0.001
cFWE = cluster FWE	MNI = Montreal Neurological Institute	AAL = Automated Anatomical Labeling				

**Table 4** Functional connectivity of the STG/insula cluster to other brain areas for subjects in the FEP group (n = 38). The colour bar indicates T-values.



**Figure 2** (a) Brain regions showing reduced hubness in the FEP ( $n = 38$ ) group compared to HCs ( $n = 31$ ) (yellow), (b) Functional connectivity of the STG/insula cluster to other brain areas for subjects in the FEP group ( $n = 38$ ). The colour bars indicate T-values.

#### 2.8.4 Effect of conceptual disorganization on bDC

In patients with high P2 compared to low P2, we observed a significant increase in bDC of a medial superior parietal cluster, comprising of paracentral lobule and precuneus regions. Results are shown in Table 5 and Figure 3 (a).

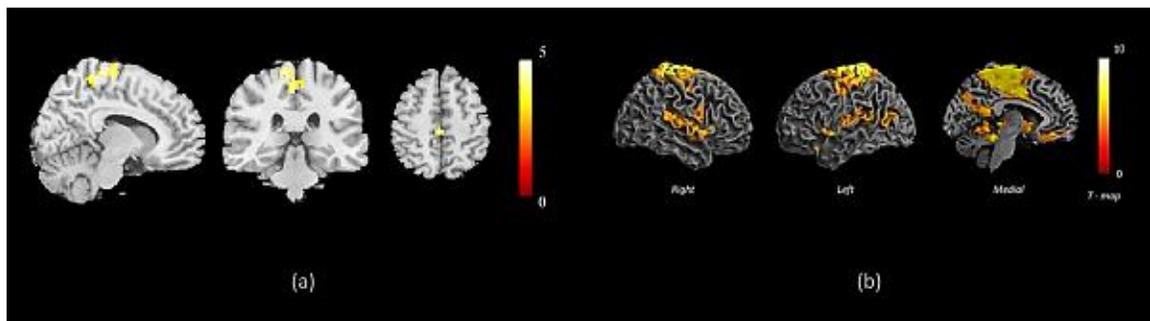
Cluster information		Peak voxel statistics				
Brain regions included in cluster (AAL labels)	Cluster size	Peak MNI coordinates			T- value	p-value (cFWE corrected)
		x	y	z		
<i>High P2 &gt; Low P2</i>						
<i>Medial superior parietal lobule cluster</i>	88	-12	-30	69	4.93	< 0.001
Paracentral_Lobule_R/L	59					
Precuneus_R/L	17					
cFWE = cluster FWE		MNI = Montreal Neurological Institute			AAL = Automated Anatomical Labeling	

**Table 5** Brain regions showing reduced hubness in the High P2 group (n = 12) compared to the Low P2 group (n = 26).

In patients with FEP as a group, the medial superior parietal cluster showed significant functional connectivity with a cluster comprising of the post/precentral regions, middle cingulate cortex and SMA, as well as bilateral STG and right middle temporal gyrus. This indicates that the region showing increased hubness among patients with high degree of disorganization is functionally connected to sensorimotor (post/precentral regions), motor planning and control (middle cingulate cortex and SMA) regions and to a limited extent, to language processing regions (bilateral STG and right middle temporal gyrus) in patients (Table 6 and Figure 3 (b)).

Cluster information		Peak voxel statistics				
Brain regions included in cluster (AAL labels)	Cluster size	Peak MNI coordinates			T-value	p-value (cFWE corrected)
		x	y	z		
<i>Precuneus/SMA cluster</i>	4838	-12	-27	75	9.45	< 0.001
Postcentral_R/L	351					
Precuneus_R/L	342					
Cingulum_Mid_R/L	279					
Precentral_R/L	261					
Paracentral_Lobule_R/L	255					
Supp_Motor_Area_R/L	233					
<i>Gyrus rectus cluster</i>	195	9	30	-21	7.94	< 0.001
Rectus_R/L	55					
Frontal_Med_Orb_R	50					
<i>Sup. Temporal gyrus cluster</i>	466	54	-18	6	8.39	< 0.001
Temporal_Sup_R/L	247					
<i>Middle temporal gyrus cluster</i>	130	51	-66	9	7.07	< 0.001
cFWE = cluster FWE	MNI = Montreal Neurological Institute	AAL = Automated Anatomical Labeling				

**Table 6** Functional connectivity of the medial superior parietal lobule cluster to other brain areas in the FEP group (n = 38).



**Figure 3** (a) Brain regions showing reduced hubness in the High P2 group (n = 12) compared to the Low P2 group (n = 26). (b) Functional connectivity of the medial superior parietal lobule cluster to other brain areas in the FEP group (n = 38). The colour bars indicate T-values.

### 2.8.5 Specificity of findings to disorganization

To test the specificity of the relationship between CD and increased bDC of medial SPL cluster, we extracted the principal eigenvariate of bDC from this cluster for each patient, and related this to individual symptom scores (P1, P3, N1, N4, N6, G5, G9), DSST score, SOFAS, mean framewise displacement, age and CGI severity score, using Spearman's correlation test. There were no significant correlations (uncorrected p ranging from 0.13 to 0.75). Furthermore, there were no systematic differences in the distributions of clinical and demographic variables (other than P2 scores) between the two groups of patients.

We observed a significant relationship between P2 scores and bDC of medial superior parietal cluster (Spearman's  $\rho=0.42$ ,  $p=0.009$ ), confirming that the observed results are not influenced by the cut-off used to identify highly disorganized FEP subjects.

We did not find any significant differences in the functional connectivity between the high P2 and low P2 groups on a two sample t test, indicating that the increase in hubness of the paracentral cluster in high P2 group is not driven by any localised aberrations in connectivity.

### 2.8.6 Discussion

To our knowledge, this is the first voxel-wise whole brain study investigating the neural basis of acute conceptual disorganization. In an acutely psychotic sample representative of the minimally treated patients with first episode psychosis, we report the following 3 major findings using ultra high-field 7T resting-state fMRI data: (1) Patients with acute first-episode psychosis (FEP) show reduced hubness of the right superior temporal cortex, a region that is functionally coupled to many other established cortical hubs (insula, midcingulate cortex, thalamus and dorsolateral prefrontal cortex), (2) Highly conceptually disorganized patients, compared to those with lower levels of disorganization, demonstrate a significant increase in the hubness of medial superior parietal region that is functionally coupled to sensorimotor regions (3) This pattern of increased hubness observed in a task-

free resting state among the acutely symptomatic FEP patients is specific to the symptom of conceptual disorganization, not influenced by other positive/ negative symptoms or degree of reduced functioning among patients.

Our observation of reduced hubness affecting superior temporal gyrus and insula is consistent with our prior work in a medicated sample of patients with schizophrenia (Palaniyappan & Liddle, 2014). In that previous study, we also observed increased hubness in the hippocampus, thalamus, inferior temporal and occipital regions in patients with schizophrenia compared to healthy controls. In the current acutely psychotic, early stage sample, the lack of any increased hubness in FEP indicates that the emergence of such peripheral hubs in visual cortex and medial/inferior temporal regions may be a feature of chronicity or treatment effect rather than being a feature of psychosis per se.

We observed an association between increased hubness of paracentral/medial superior parietal region that is not conventionally regarded as a functional hub and conceptual disorganization. Interestingly, this cluster was functionally connected to the superior and middle temporal regions as well as regions comprising the sensorimotor network (Dosenbach et al., 2010). Assuming that the pathophysiology of psychosis is a generalized dysconnectivity that has a preponderance to affect regions such as STG due to their higher hubness, one would not expect to see an increased hubness of peripheral, sensory nodes in a subgroup of patients. In this context, our results reaffirm the notion that distinct pathophysiological processes are likely to underlie the myriad of symptoms seen in psychosis.

In so far as functional connectivity reflects the ability to transmit information across distant brain regions, it is possible that the emergence of peripheral (sensory) hubs could be a compensatory mechanism to preserve brain function. This may result in a re-routing of information transmitted via functional brain networks (Palaniyappan, 2017). Such re-routing could result in an aberrant shunting of associative processes (in line with Wernicke's notion of sejunction (Franzek, 1990)), resulting in disorganized speech. While we cannot disentangle the compensatory changes from the causally influential changes in

the present study, longitudinal tracking of the symptom course as well as change in hubness will clarify this issue.

While most previous studies that recruited patients with persistent disorganization in later stages of illness implicated a role for the language processing regions, we note STG hubness to be reduced in both high and low P2 groups. It is worth noting that the extant literature implicating language regions in thought disorder sought changes in language network a priori, rather than taking a discovery approach without task constraints. Cavelti et al., 2017 and Sumner et al., 2018 could identify only 2 resting state fMRI studies investigating this issue, despite their exhaustive search. Interestingly, these few whole brain studies have reported sensorimotor dysconnectivity in association with thought disorder. It is also important to note that STG changes seen in patients with psychosis are not specific to thought disorder (Sumner et al., 2018). For instance, a large body of structural and functional studies implicate STG in negative symptoms (Fischer et al., 2012; Li et al., 2018), as well as auditory hallucinations (Modinos et al., 2013, Palaniyappan et al., 2012). Our findings support the notion that language network dysfunction is likely to be a common feature across the various symptomatic subgroups of psychosis, at least in the early, untreated stages of illness.

We wish to highlight that our observation does not necessarily negate a role for language network in thought disorder; instead it provides empirical support for a role of system-level dysconnectivity at resting-state as a determinant of the severity of FTD. Our results are not directly comparable to the results obtained from studies on patients with persistent thought disorder. Ketamine challenge which recapitulates acute thought disorder, has been reported to increase functional (BOLD) activity in the same medial sensory association cluster where we observed higher level of bDC among the more disorganized patient group (Deakin et al., 2008). A white fiber bundle recognized to participate in language production (Asami et al., 2013) connects the sensory association cortex to auditory association cortex (Wang et al., 2012). Our functional connectivity analysis also revealed a significant relationship between superior and middle temporal areas and the medial cluster located on the sensory association area in patients with FEP. It is possible that the primary

‘downstream’ interference caused by an emergent hub in the sensory association cortex is mediated via the language network.

To conclude, in the presence of reduced hubness of the superior temporal hub region, a relative increase in the hubness of sensory association regions is seen in highly disorganized patients with FEP. We postulate that an inefficient cortical information transfer resulting from the emergence of peripheral hubs underlies the pathogenesis of disorganization among patients with psychosis.

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## 2.10 Supplementary information

### Appendix 1 Results from a two-sample t-test (FEPs vs. HC) of weighted degree centrality (wDC) maps

We found a similar reduction in weighted degree centrality in the STG/Insula cluster with same coordinates ( $x = 48$ ,  $y = -9$ ,  $z = 3$ ) for the peak of the cluster and same peak statistics ( $T = 5$ ,  $p = 0.001$ ) as observed for the two sample t-test results of our binarized degree centrality maps (Table 7).

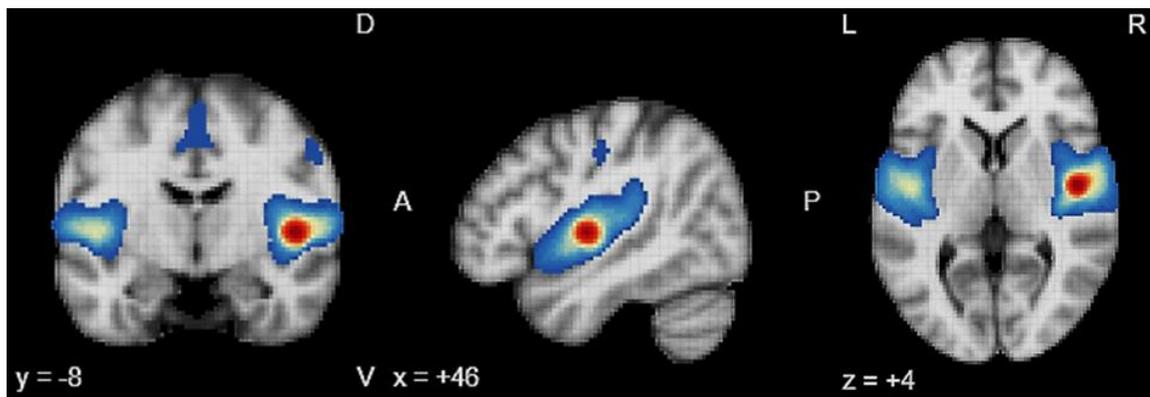
Cluster information		Peak voxel statistics				
Brain regions included in cluster (AAL labels)	Cluster size	Peak MNI coordinates			T- value	p-value (cFWE corrected)
		x	y	z		
<u>FEP &lt; HC</u>						
<i>STG/Insula cluster</i>	201	48	-9	3	5.00	0.001
Temporal_Sup_R	88					
Insula_R	56					
Heschl_R	16					
<u>FEP &gt; HC</u>						
Not significant						
cFWE = cluster FWE	MNI = Montreal Neurological Institute	FEP = First episode psychosis	HC = Healthy controls			

**Table 7** Brain regions showing wDC alterations in the FEP group ( $n = 38$ ) compared to the HC group ( $n = 31$ ).

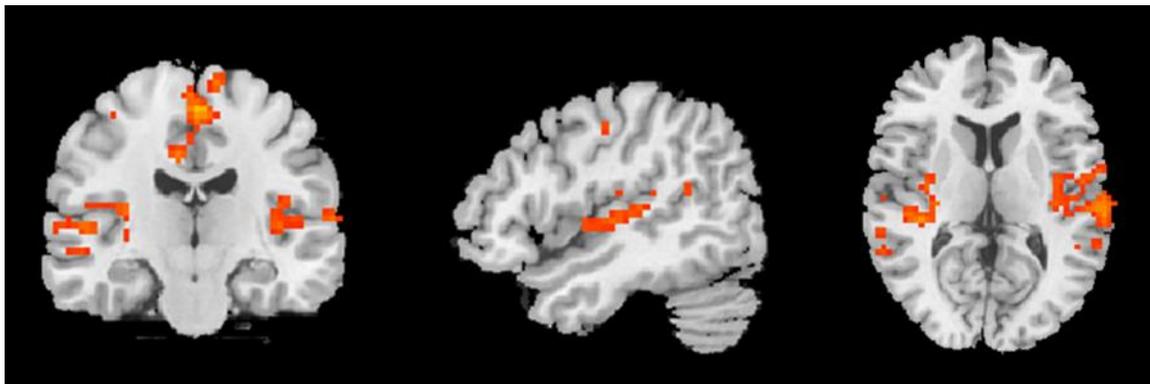
### Appendix 2 Neurosynth meta-analyses

For the STG/Insula cluster

After obtaining functional connectivity maps of the STG/Insula cluster (showing reduced hubness in the patients vs. healthy controls) with the rest of the brain for healthy controls, we wanted to assess the comparability of our results with those observed in previous literature. We searched the Neurosynth online database ([www.neurosynth.org](http://www.neurosynth.org)) for meta-analytic maps of functional connectivity of the cluster belonging to that coordinate ( $x = 48, y = -9, z = 3$ ). Our observations of the brain regions which were functionally connected to the STG/Insula cluster were similar to findings from the existing literature, confirming the comparability of our study to the literature (Figures 4 & 5).



**Figure 4** Meta-analytic results (obtained from the Neurosynth database) of functional connectivity associations between the STG/Insula cluster and the rest of the brain.

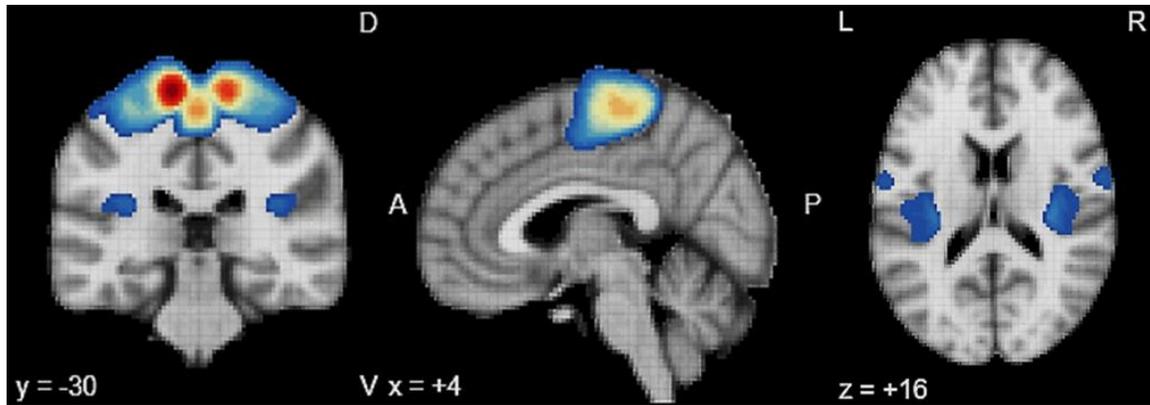


**Figure 5** Functional connectivity associations between the STG/Insula cluster and the rest of the brain.

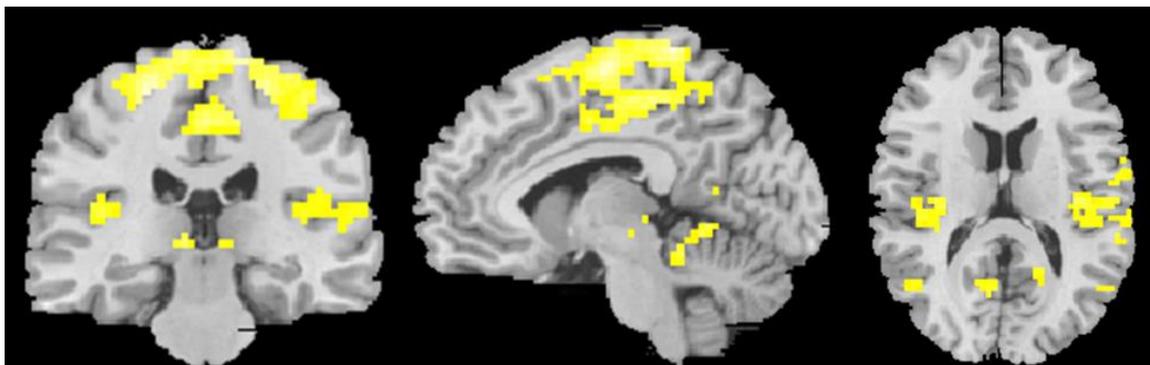
#### For the medial superior parietal cluster

We performed a similar comparability check for the mSPL cluster showing increased hubness in the patient group with high disorganization vs. the patient group showing low

disorganization. Results from the meta-analytic maps of functional connectivity of the cluster belonging to that coordinate ( $x = -12, y = -30, z = 69$ ) showed similarities to our findings of functional connectivity (Figures 6 & 7).



**Figure 6** Meta-analytic results (obtained from the Neurosynth database) of functional connectivity associations between the medial superior parietal cluster and the rest of the brain.



**Figure 7** Functional connectivity associations between the medial superior parietal cluster and the rest of the brain.

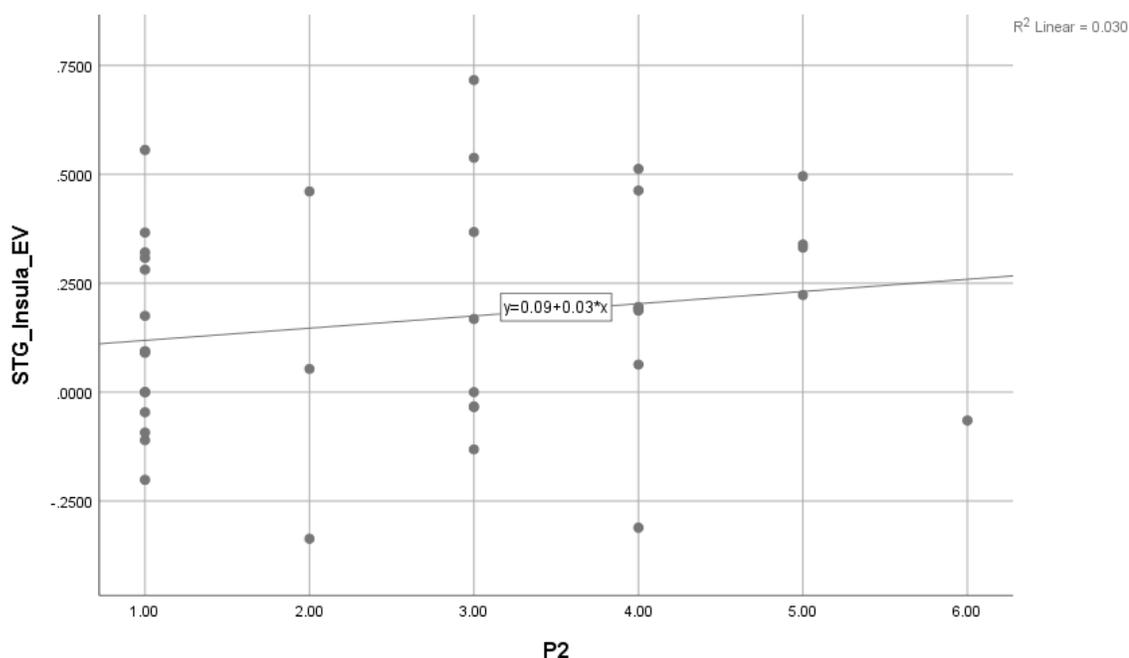
### Appendix 3 Correlation between eigenvariate of STG/Insula and mSPL

We wanted to determine how the hubness properties of the STG/Insula cluster and medial superior parietal clusters were correlated and whether an increase or decrease in hubness of one cluster predicted the hubness properties of the other cluster. We extracted the eigenvariate of the two clusters and performed a bivariate correlation analysis between them. Results of the analysis show a significant positive correlation between the clusters, suggesting that an alteration in degree centrality of the STG/Insula is related to the alteration in hubness of the medial superior parietal cluster. In our results, we observe a decrease in hubness of the STG/Insula cluster but whether that predicts a decrease in hubness of the medial superior parietal cluster is not clear.

Patients (FEP group)	mSPL eigenvariate	
	Spearman's rho	p-value
STG/Insula eigenvariate	0.424	0.008

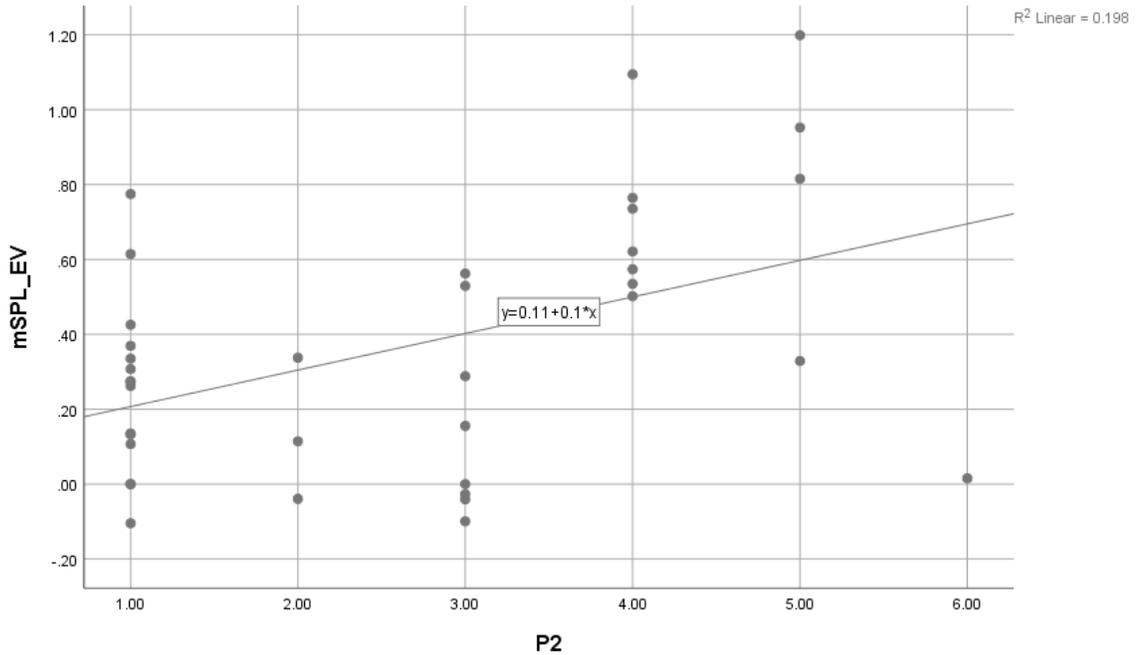
**Table 8** Correlation between the eigenvariates of STG/Insula and mSPL clusters in the FEP group

#### **Appendix 4 Scatterplots between the P2 scores and eigenvariate of the STG/Insula and mSPL clusters**



**Figure 8** Relationship between eigenvariate of the medial superior parietal cluster and conceptual disorganization scores.

We observed a positive relationship between the P2 scores (X-axis) and the eigenvariate of the STG/Insula cluster (Y-axis) as shown in Figure 8. The scatterplot suggests that an increase in the severity of P2 (conceptual disorganization) is associated with an increase in hubness of the STG/Insula cluster. Therefore, in patients with high conceptual disorganization, we would expect the STG/Insula cluster to act like a functional hub of the healthy control group which could explain the lack of findings of any differences in degree centrality between the healthy controls and the High P2 group. However, some points on the scatterplot do not follow the relationship depicted by the line of best fit. We would expect to see a collinear relationship between low P2 scores and low STG/Insula hubness and High P2 scores and high STG/Insula hubness. However, some patients (points on the graph) exhibit low P2 scores but high STG/Insula hubness and vice-versa. Therefore, the relationship between the eigenvariate of the STG/Insula cluster and P2 scores do not present a conclusive relationship.



**Figure 9** Relationship between eigenvariate of the medial superior parietal cluster and conceptual disorganization scores.

We observed a positive relationship between the P2 scores (X-axis) and the eigenvariate of the mSPL cluster (Y-axis) as shown in Figure 9. The scatterplot suggests that an increase in the severity of P2 (conceptual disorganization) scores is associated with an increase in hubness of the mSPL cluster. However, most FEPs show high hubness of the mSPL cluster at different values of the P2 scored item. From this relationship we would expect to confirm that conceptual disorganization is a persistent feature of psychosis and is associated with increase in the hubness of the mSPL brain region. There are, however, a few subjects who show reduced hubness properties of the mSPL cluster at a low severity of conceptual disorganization. This suggests that there is no reorganization of cortical networks occurring in these subjects as a result of the decrease in hubness of the STG/Insula region. There are 2 subjects which depict reduced hubness in the mSPL cluster with high conceptual disorganization, which suggests that in these subjects the mSPL cluster either

does not show any hubness alterations or reduces in hubness after the initial compensatory increase in hubness, therefore behaving like a functional hub in the healthy brain.

### 2.10.1 References:

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## 2.12 Conflict of interest

LP receives book royalties from Oxford University Press and income from the SPMM MRCPsych course. In the last 5 years, his or his spousal pension funds held shares of Shire Inc., and GlaxoSmithKline. LP has received investigator initiated educational grants from Otsuka Canada and Janssen Canada in 2017 and a speaker fee from Otsuka Canada in 2017 and Canadian Psychiatric Association in 2018. LP and KD received support from Boehringer Ingelheim to attend an investigator meeting in 2017. All other authors report no potential conflicts of interest.

## 2.13 Acknowledgements

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## Chapter 3: *General discussion*

### 3 Conclusions

The aim of the current study was to investigate the theory of ‘dysconnection’ (Friston & Frith, 1995) in an acutely psychotic patient sample. A reduction in hubness of the STG/Insula region in relation to the symptoms of conceptual disorganization (and the association of this region to other regions involved in sensory and executive functioning) helps explain the theory of ‘dysconnection’ in distributed brain networks in first episode psychosis. These results are consistent with previous work in a medicated sample of patients with schizophrenia (Palaniyappan & Liddle, 2014). In that previous study, increased hubness was also observed in the hippocampus, thalamus, inferior temporal and occipital regions in patients with schizophrenia compared to healthy controls. In the current acutely psychotic, early stage sample, the lack of any increased hubness in FEP indicates that the emergence of such peripheral hubs in visual cortex and medial/inferior temporal regions may be a feature of chronicity or treatment effect rather than being a feature of psychosis per se.

Furthermore, increased hubness of the medial superior parietal (mSPL) cluster—in the group with a high severity of conceptual disorganization— provides evidence of an abnormal reorganization occurring in cortical networks. Conventionally, this brain region is not regarded as a functional hub. This speaks to an adaptive mechanism to counterbalance the reduced hubness observed in the overall patient group. Interestingly, this cluster was functionally connected to the superior and middle temporal regions as well as regions comprising the sensorimotor network (Dosenbach et al., 2010). We, therefore, conclude that a generalized dysconnectivity of the STG/Insula cluster might explain the underlying pathophysiology of psychosis. Specifically, the observation of increased connections in the peripheral sensory brain regions (mSPL) could explain the distinct pathophysiological processes that are likely to underlie the multifaceted nature of the symptoms of psychosis. The compensatory hubness increase in the peripheral sensory brain region may suggest the emergence of alternate routes for the transmission of information, via functional brain networks, as an activity to preserve brain function (Palaniyappan, 2017). This re-routing could result in an aberrant shunting of associative

processes (Wernicke's notion of sejunction (Franzek, 1990)) —explaining the core symptoms observed in psychosis.

Graph theory has, therefore, been very useful in studying brain network alterations in early-stage as well as established psychosis at the level of a microscopic voxel. Previously, graph theory has been successful in demonstrating abnormalities in a sample comprising of patients with chronic schizophrenia (Zalesky et al., 2011; Palaniyappan & Liddle, 2014; Yu et al., 2015; Cheng et al., 2015; Cao et al., 2016; Kambeitz et al., 2016; Palaniyappan et al., 2018). However, careful consideration is necessary when using graph metrics as diagnostic measures or as tools to predict the future functional outcomes of psychosis. This is because a single graph metric would both be insufficient in the characterization of aberrations in functional brain networks and might not consider the dynamically changing topological properties of brain networks when explaining these network alterations (De Vico Fallani et al., 2014). This suggests the need for using other mathematical models (e.g., dynamic causal modelling (Friston, 2003) and Granger causality analysis (Granger, 1969)) alongside graph theory which would be useful to predict brain activity at a future time point based on patterns of brain activity at the present and previous time points. This approach would also be helpful to map the directionality of information processing, not only in terms of top-down and bottom-up processing streams but also in terms of the sequential recruitment of brain areas in either performing a task or maintaining internal homeostasis.

One limitation of this study is the difficulty in delineating the specificity of these compensatory changes occurring as a result of the causally influential decrease in connectivity. To delineate the specificity of these compensatory changes, future works should include a longitudinal characterization of brain networks at follow-up time points (e.g. at 6 and 12 months). This would allow us to identify the effects of the severity and duration of the symptoms on the patterns of altered connectivity across the whole brain. Furthermore, a cross-sectional analysis of altered hubness in patients with established psychosis compared to healthy controls would be useful to confirm that our findings are comparable to the observations in the existing literature. It is important to note here that for the HCs in our sample the FC between the whole brain and both the STG/Insula and

mSPL clusters is similar to the evidence obtained from the meta-analytic literature on the FC of these two regions, suggesting the relevance of our findings to further the goal of establishing the neural basis of established psychosis. In addition, these results provide a limited understanding of the extent of these hubness alterations which is a second limitation of this study. To identify the extent of DC alterations, it would be beneficial to employ a region-of-interest (ROI) approach to characterize and compare functional networks in both patients and controls. A major advantage of using this approach would be a reduction in the size of adjacency matrices (moving from a voxel-wise approach to an ROI-based approach) used to characterize graph metrics (e.g. degree centrality (DC)). This would reduce the computational complexity of a multidimensional dataset. Another advantage of this approach would be estimating DC alterations in a single subject (as opposed to the entire group) by comparing the DC maps of an individual patient and the entire HC sample. The measure of ‘Hub Disruption Index’ (proposed by Achard et al., 2012), which determines the functional reorganization occurring in resting-state brain networks, could be helpful for such an estimation. However, the estimation of the extent of FC alterations and cortical reorganizations for individual patients is highly sensitive and variable in nature due to several reasons (e.g., the inter-subject variability of the psychopathological domains and the number of voxels within a particular ROI). Addressing these two limitations in our current study could help characterize functional brain networks in unmedicated first-episode psychosis as well as provide insight into the progressive changes which occur as a characteristic feature of established psychosis.

With regards to the related construct of FTD in psychosis, our study lacked instruments such as the Thought and Language Index (TLI) which comprehensively quantify the various aspects of FTD (Kircher et al., 2018; Strik et al., 2010). As a result, the functional correlates of hemodynamic (BOLD) activation in relation to the symptoms of FTD were not investigated in this study. However, our non-investigation of the neural correlates of FTD (and observations of aberrant FC in relation to CD) does not necessarily negate the importance of studying the language network in thought disorder; instead, it provides empirical support for the need to investigate a system-level dysconnectivity occurring at resting-state as a determinant of the severity of FTD. It would, therefore, be helpful to obtain scores for individual items on the TLI assessment tool for all individuals and

investigate the functional connectivity patterns which explain the multifaceted nature of FTD in psychosis. Although the individual items of formal thought disorder (Thought, Language and Communication scales) and conceptual disorganization (PANSS) have both been used to measure disorders in thought processes associated with psychosis, no significant correlations were observed between these items in terms of their respective scores for individual subjects (Docherty, 2012). Testing the functional dependence of both these measures (by correlating individual functional connectivity correlates of FTD and CD) would thus be interesting to assess the reliability of the construct of FTD as a measure of disorganization. Since the current study was focused on studying patients with first episode psychosis, our observations are not directly comparable to the results obtained from previous studies on patients with persistent thought disorder.

One of the strengths of our study is the use of an ultra-high field (UHF) magnet of field strength 7T to scan the study participants. Using an ultra-high field (UHF) over traditional field strengths (1.5 T / 3 T) can have many advantages such as a better spatial resolution of the MR images. UHF can help resolve the difficulties in the assessment of structural and functional complexities of the human brain at various spatial resolutions. With an increase in field strength, it is possible to increase the signal-to-noise ratio (SNR) as well as the contrast-to-noise ratio (CNR) of the MR signal —therefore increasing the resolution of the scanned image (Duyn, 2012). A multiband acceleration factor (MB = 3) was also included in the functional (rs-fMRI) acquisition protocol for our study. This is an advantage over other standardized protocols because this technique effectively shortens acquisition time (without decreasing either the echo time (TE) or SNR) by the simultaneous acquisition of multiple slices. In terms of the implications of using a multiband acceleration factor for rs-fMRI data, analyses have revealed significantly increased levels of sensitivity in the detection of RSNs (Preibisch et al., 2015).

Another strength of our study is the inclusion of unmedicated patients in their first episode of psychosis. This implies that our findings (of aberrant functional connectivity of distributed brain regions) point towards the functional basis of psychosis and that they are specific to the symptom of conceptual disorganization observed in psychosis, not

influenced by other positive/ negative symptoms or degree of reduced functioning among patients.

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